Report of the NCI-CDC Working Group to Revise the 1985 NIH Radioepidemiological Tables

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Overview

An example of quantitative uncertainty analysis (QUA)

- Ionizing radiation is a known and well-quantified cancer risk factor
- Risk estimates are uncertain
- But we know a lot about these uncertainties
- And we can address implications for risk

Elements of the approach

Take a problem apart

Identify component parts

Evaluate their uncertainties and how they fit together

Evaluate the overall uncertainty of the solution

A “warts and all” presentation of relevant mainstream science

Advantage of transparency, and consequent credibility

- But can’t address every possible source of uncertainty

A good way to focus attention on critical areas, where better information may be needed

Legal Basis for Adjudication of (Some) Compensation Claims

QUA mandated in the US for adjudication of some claims against the government for radiation-related cancer

Energy Employees' Occupational Illness Compensation Program Act of 2000 (EEOICPA), P.L. 106-398

Rationale

- We know a lot about radiation-related cancer risk in exposed populations
- We can estimate site-specific ERR, by exposure history and age following exposure
- In an exposed population, the proportion of cancers that would not have occurred in the absence of exposure is estimated by Assigned Share = ERR/(1+ERR)
- This population quantity can be used as a guide for adjudication of individual cases
- Note AS < 0.5 if and only if ERR < 1.0

NIH Radio-Epidemiological Tables
Background

1985 NIH report: Congressional mandate (P.L. 97-414)

- Requiring periodic update
- Essentially, summary of mainstream scientific information
- VA the main user: claims based on service-related exposure

EEOICPA: Dept. of Energy and DOE contractor workers

- NIOSH, DOL

Interesting problem in quantitative uncertainty analysis applied to radiation-related risk

- Implications for radiation protection and informed consent

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Present Use

Department of Veterans Affairs (VA)

- Uses tables to adjudicate compensation claims for radiation-induced cancer
- Previously, commissioned CIRRPC to devise a screening approach based on the (difficult to use) 1985 tables
- In effect, the approach screens out claims for which the upper 99% uncertainty limit for ERR is < 50%
- EEOICPA mandates similar approach for claims related to work for DOE or DOE contractors
- NIOSH, Dept. Labor

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Reasons for Update

1985 tables report outmoded - based largely on 1980 BEIR III Report

New data

- Longer follow-up
- New A-bomb survivor doses (DS86 replaced T65D)
- RERF Tumor Registry (comprehensive incidence data)

New inferences about risk & its modifiers

Methodological advances, taking advantage of greater computing power

- More flexible modeling
- More sophisticated treatment of uncertainty

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Nature of the Update

An interim update, bridging the gap between BEIR III and BEIR VII

- Carried out by a small working group
- Based mainly on A-bomb survivor incidence data: RERF Tumor Registry (Radiation Research, 1994), & site-specific studies
- But also on other studies
  - Thyroid, radon-related lung ca

Emphasis on uncertainty

- Statistical uncertainty based on likelihood contours of fitted risk estimates

- Treatment of other sources of uncertainty follows
  - NCRP Commentary 14: A guide for uncertainty analysis in dose & risk assessments
  - NCRP Report 126: Uncertainties in fatal cancer risk estimates used in radiation protection

- Plus new treatments of latency, transfer between populations and relative effectiveness of radiations of different qualities

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General Approach

$$\text{"Assigned share"} = \frac{\text{excess risk}}{\text{total risk}} = \frac{\text{ERR}}{1+\text{ERR}}$$

"Risk" and "ERR" are properties of populations, not individuals

Use of "assigned share" in place of "probability of causation" highlights the difference

As a society, we agree to adjudicate an individual claim on the basis of this population property

-- Analogy: use of actuarial tables to allocate annuity payments

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General Approach (2)

ERR is estimated as an uncertain function of dose

-- modified by sex, exposure age, attained age

-- other factors, e.g., smoking for lung cancer

But ERR also depends upon uncertain influence of other important factors not covered by epi data

-- Uncertainty estimates for these factors largely subjective

-- Folded in with statistical uncertainty

Overall uncertainty distribution summarizes:

-- What we know about risk from epidemiological studies

-- What we think we know about how to apply that information

-- What we don't really know, but can't ignore

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Treatment of Uncertainty

Statistical variation – likelihood profile based (usually) on A-bomb survivor data

Other factors subjective to some degree

- Low-dose extrapolation of risk
- Transfer of ERR estimate from Japanese A-bomb survivors to US population

Interactive program (IREP) computes combined uncertainty by Monte Carlo simulation

Claims adjudication example

Stomach cancer at age 60 in female worker

- 0.12 Gy chronic low-LET dose to the stomach at ages 30-35
- Seeks redress from the US government

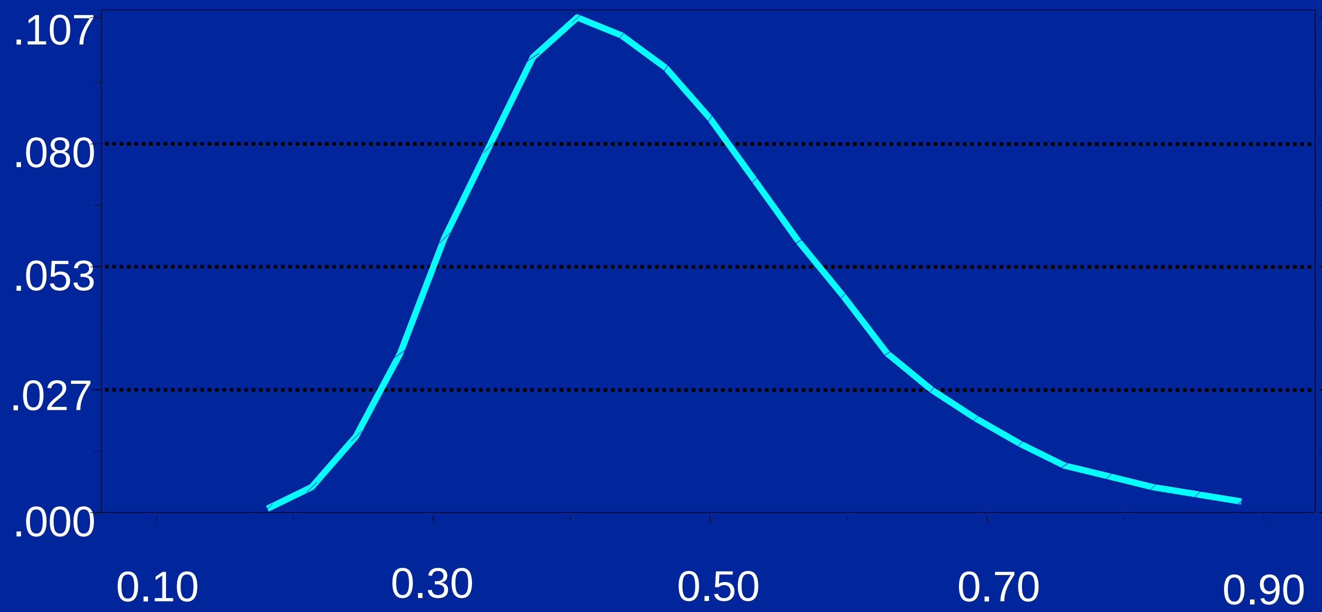
Best statistical information: LSS Tumor Registry of A-bomb survivors, 1958-1987

Correct for

- Chronic vs. acute exposure (DDREF)
- Japan-US differences in rates (population transfer)

Stomach Cancer Example

Statistical uncertainty for ERR/Sv at age 60 (lognormal, GM 0.45, GSD 1.32)



ERR per Sv

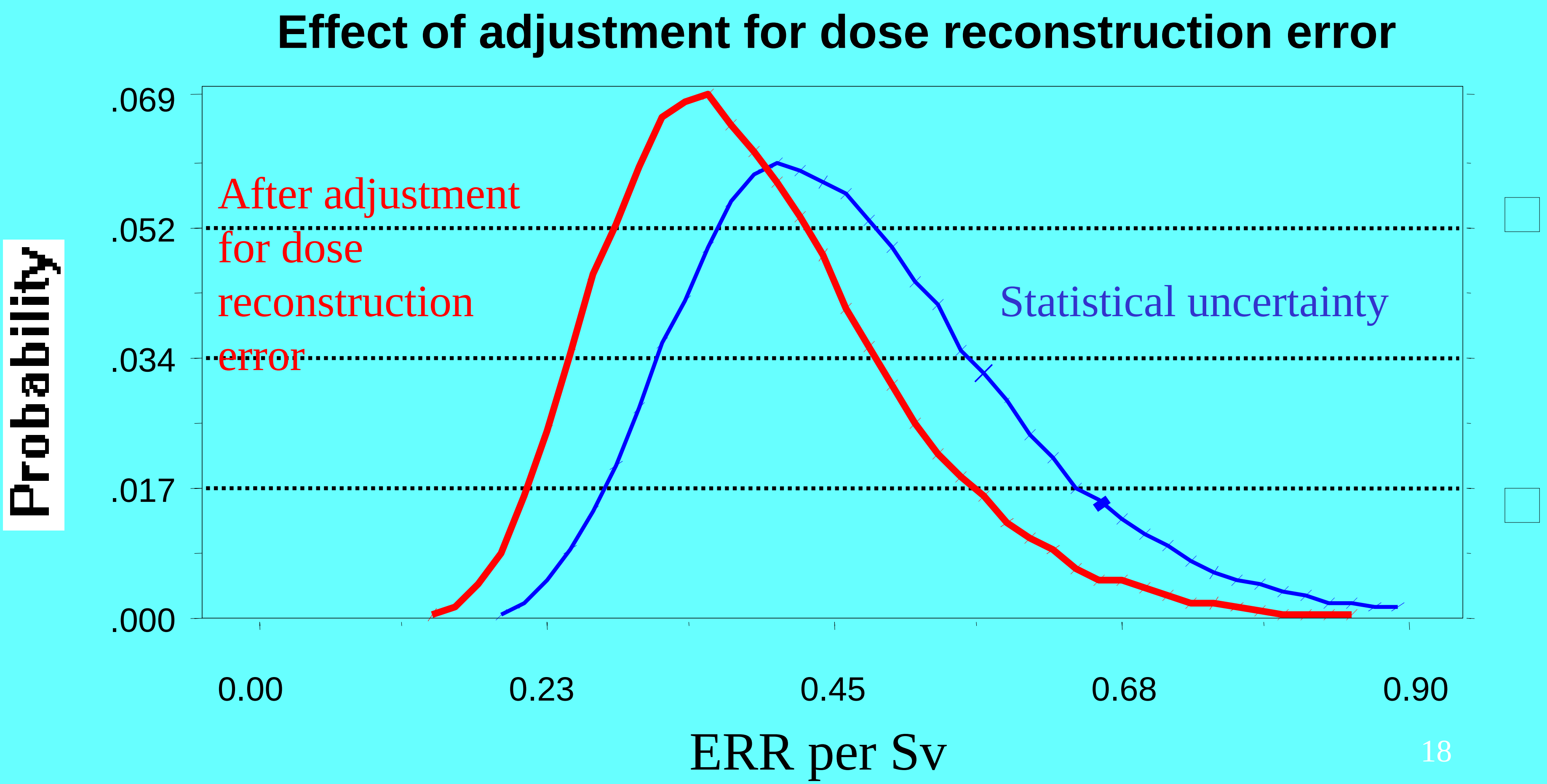
Uncertainty in dose reconstruction for A-bomb survivors (NCRP 126)

Uncertainty about

- Magnitude of random errors in individual doses
- Appropriate choice of neutron weight
- Systematic biases in (and neutron dose

Overall correction corresponds to multiplication of uncertain risk by random variable ~N(0.83,0.084)

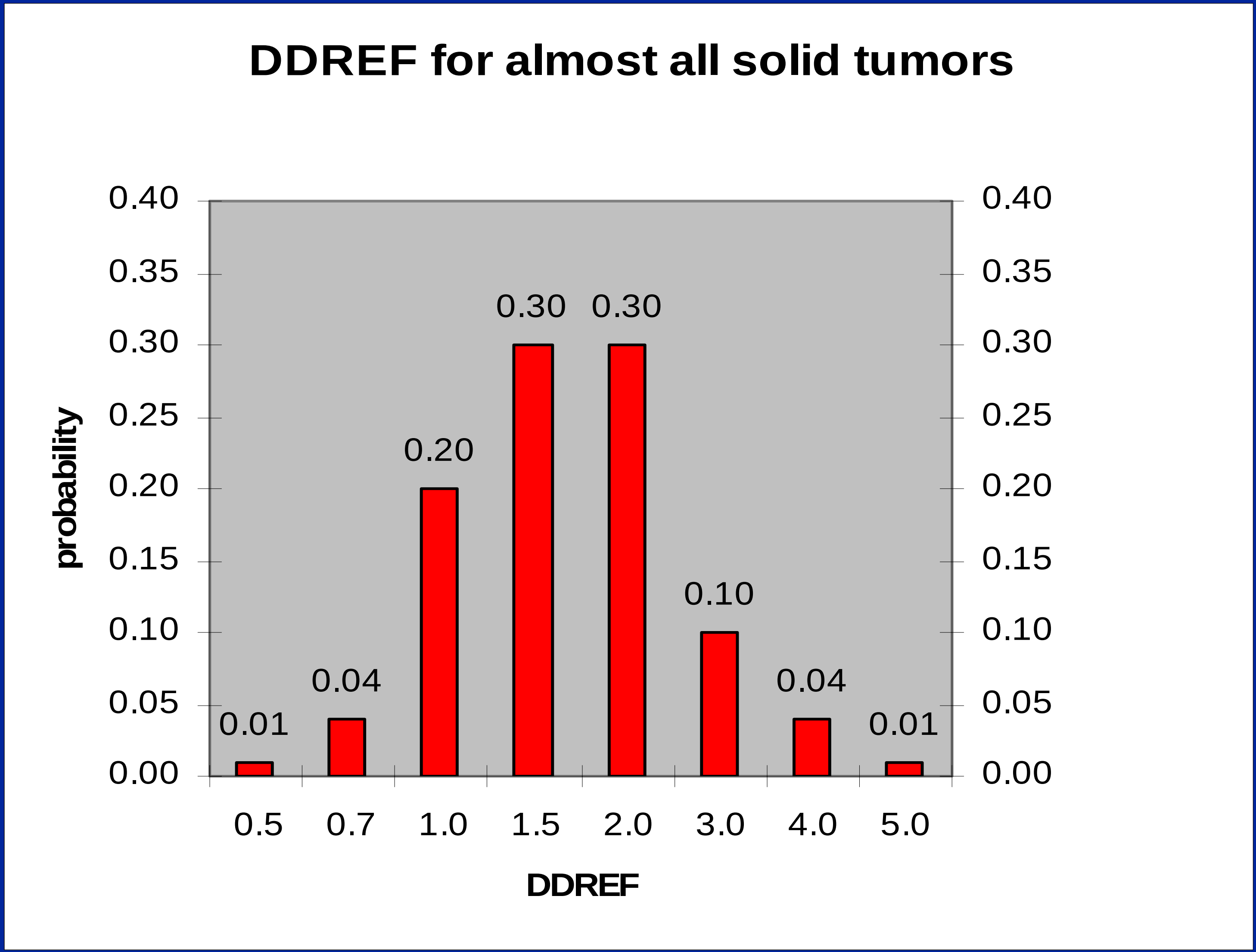
Stomach cancer example



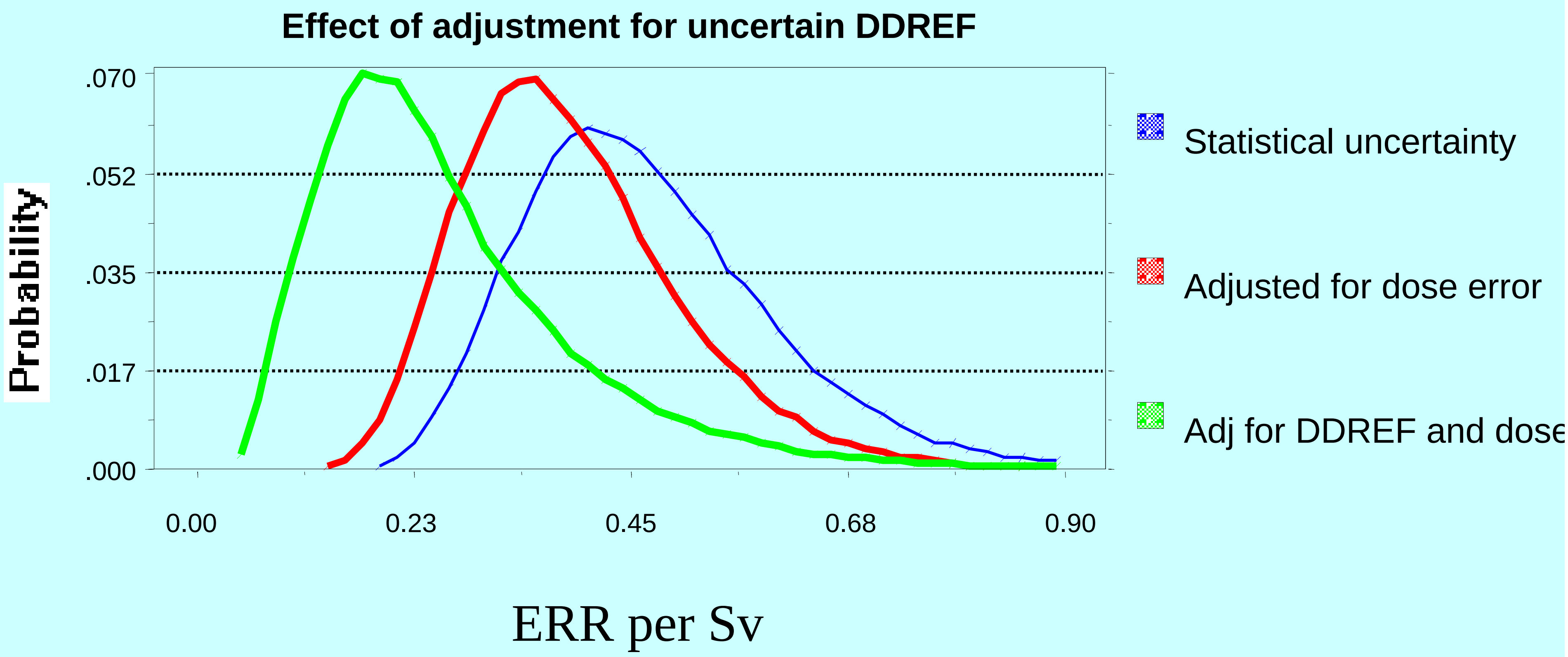
Uncertain assumption:
low-dose ERR/Sv = (high-dose ERR/Sv)/DDREF

- ERR estimated for acute, high-dose exposure
- Experimental studies suggest that risk per Sv is reduced at low doses and low dose rates
- ICRP recommends dividing ERR by fixed DDREF = 2 for radiation protection purposes
- QUA approach is to treat it as an uncertain factor (NCRP 126, EPA 1998, others)

DDREF uncertainty distribution used in IREP



Stomach cancer example, continued



Radiation Quality

Radiations of different quality deposit energy at different densities, which influence the likelihood of complex DNA damage

For example, photons from medical x ray, with energies in the 20-250 keV range, are thought to have more carcinogenic potential than (-ray photons at > 250 keV

IREP treatment of x-ray RBE

For medical x ray (photons with energy in range 30 – 250 keV)

- Assign RBE = 1 (same as high-energy photons) with probability 25%
- Assign 75% probability to lognormal distribution with 95% limits 1 - 5

Transfer to the U.S. population

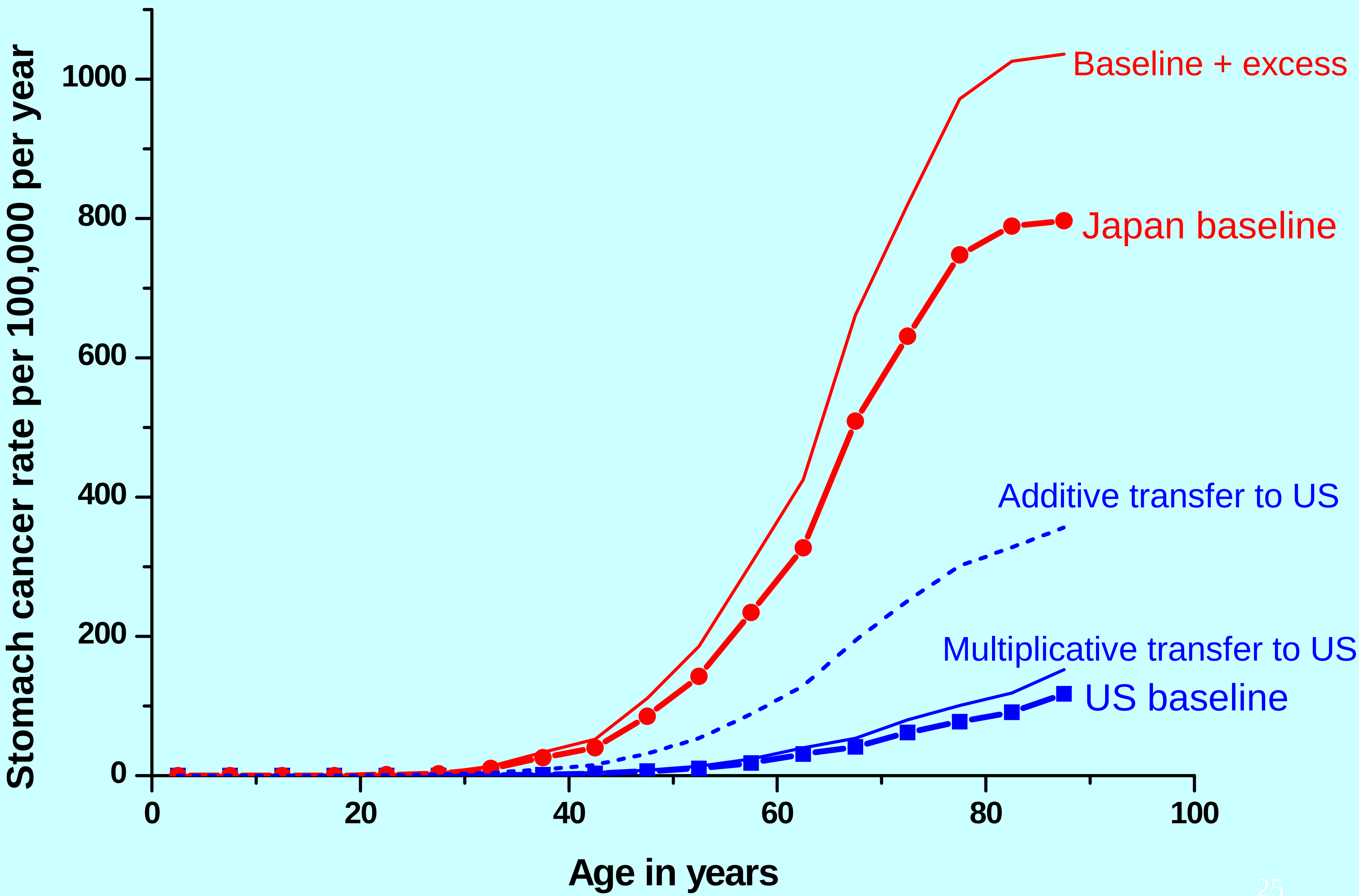
Baseline cancer rates differ between Japan and the U.S.

we don’t know the implications for radiation-related risk in the US pop.

Difference between rates is only a few percent for all solid cancers combined

But for stomach cancer, Japanese rates are 12 times those in the United States

Comparison of U.S. and Japanese Stomach Cancer Rates (Males)



How to transfer ERR estimate from Japan to the US?

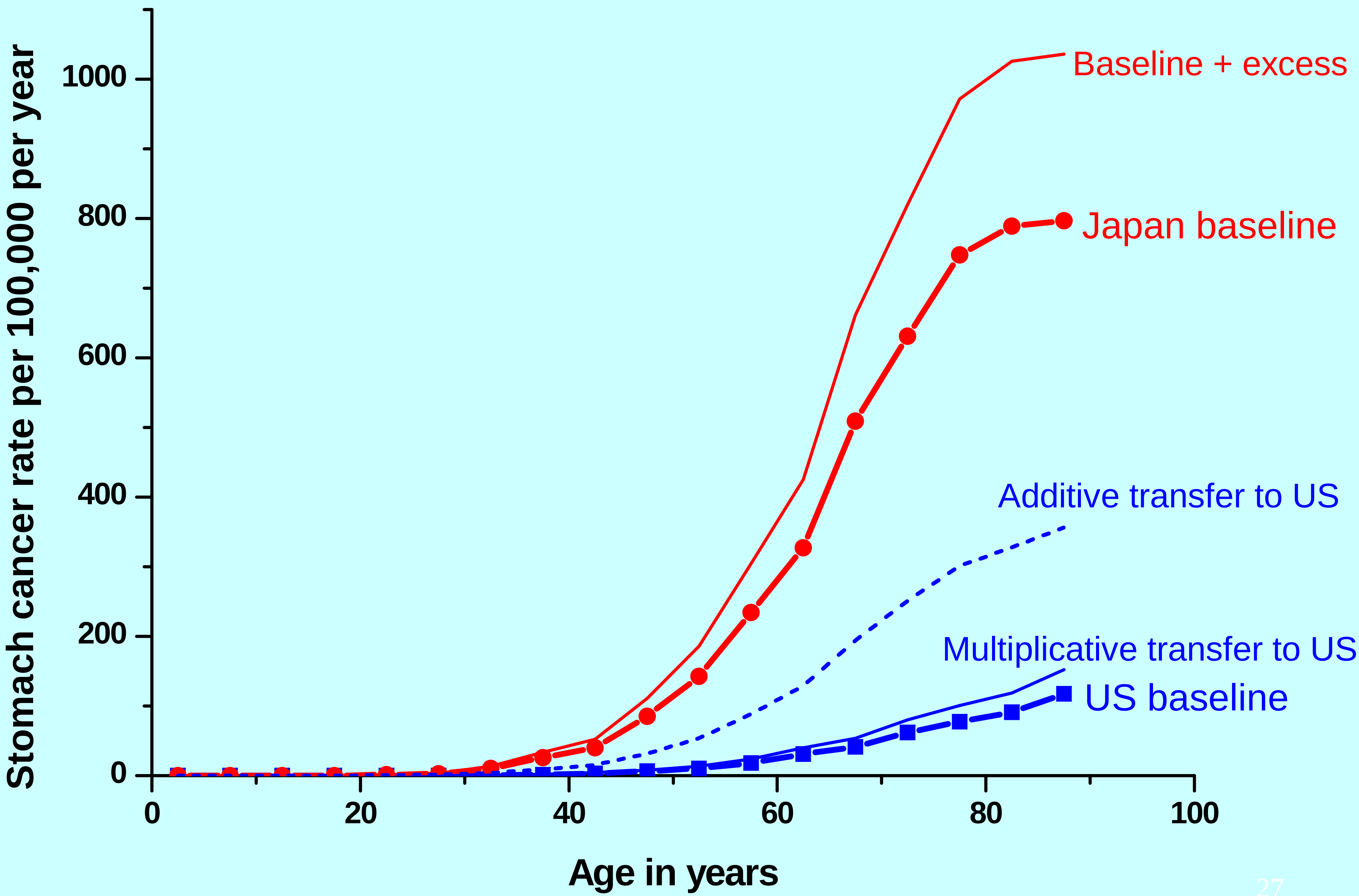
We could use the A-bomb survivor ERR

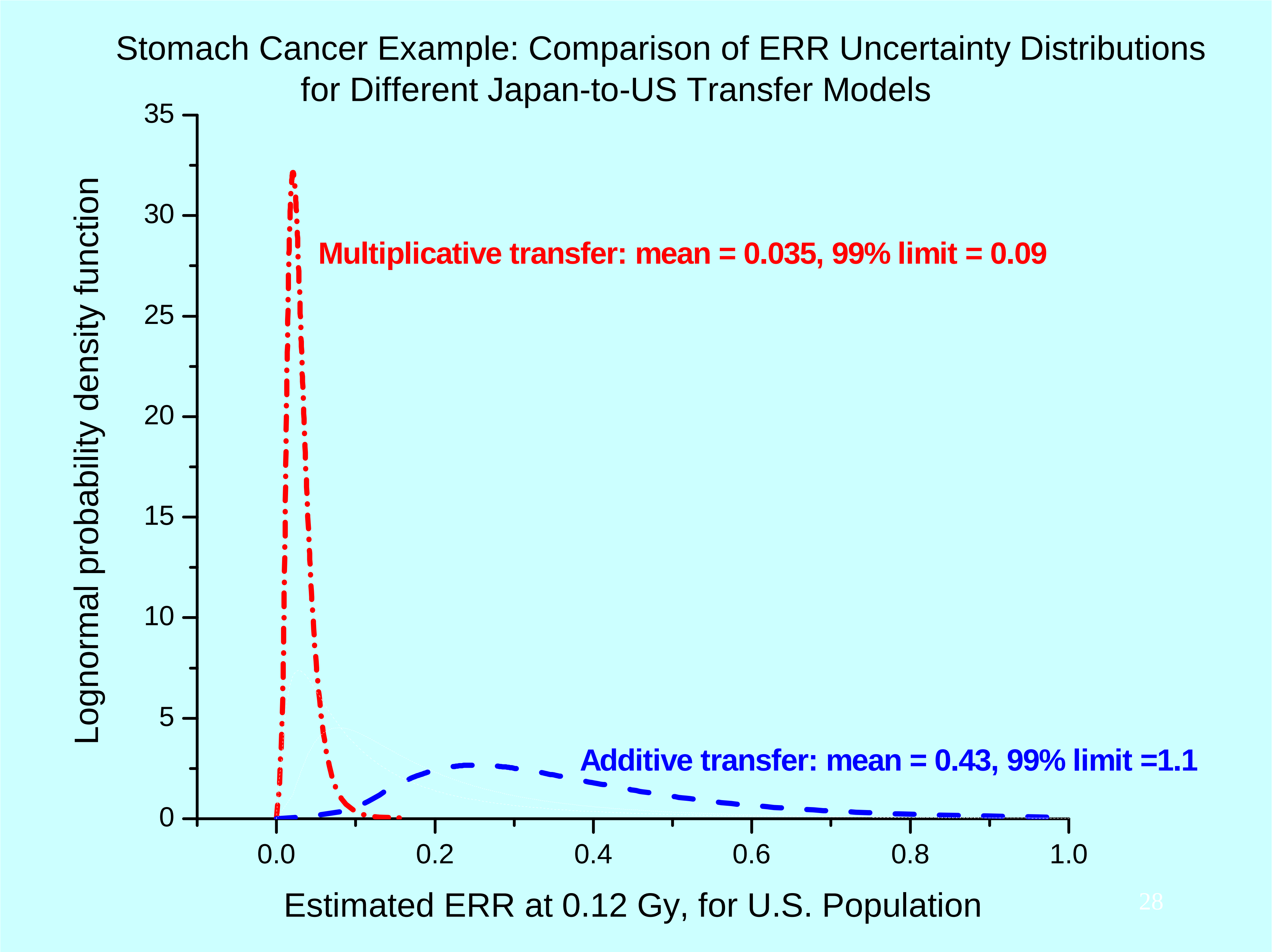
- **Multiplicative transfer – assume ratio of excess to baseline doesn't change**
- Biologically plausible if baseline rates differ because of differential exposure to promoters

Or assume the radiation-related **excess rates** (i.e., ERR H baseline) are the same

- **Additive transfer**: multiply ERR by 12
- Plausible if rates differ because of differential exposure to competing cancer initiators

Comparison of U.S. and Japanese Stomach Cancer Rates (Males)





Stomach Cancer Example: Comparison of ERR Uncertainty Distributions
for Different Japan-to-US Transfer Models
Multiplicative transfer: mean = 0.035, 99% limit = 0.09
Additive transfer: mean = 0.43, 99% limit =1.1
Lognormal probability density function
0
5
10
15
20
25
30
35
0.0
0.2
0.4
0.6
0.8
1.0
Estimated ERR at 0.12 Gy, for U.S. Population

Suppose we don't know anything

Baseline differences could reflect differential exposure to both promoters and initiators,

Consider intermediate transfer models

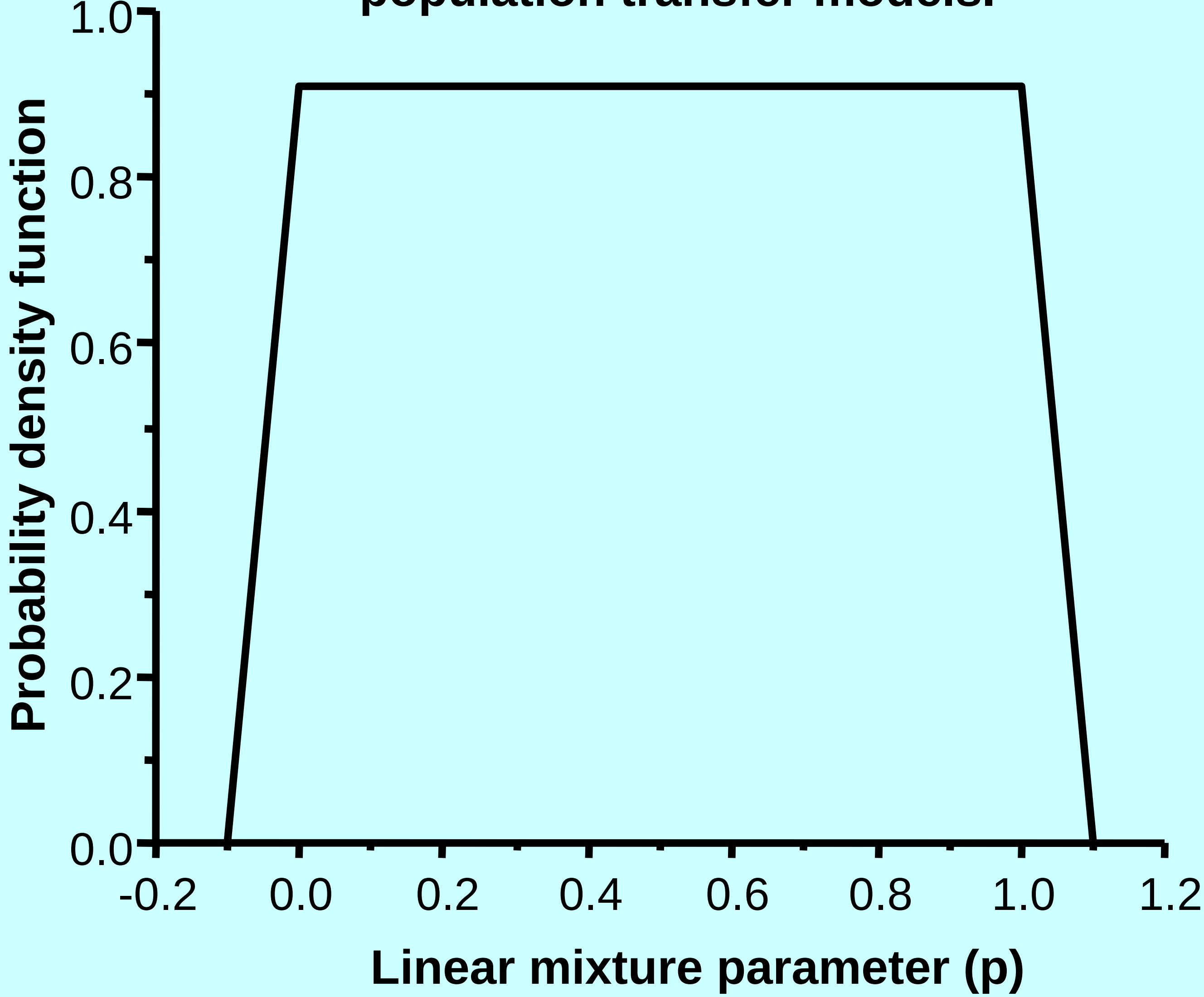
E.g., for some value p, 0 # p # 1,

- ERR(p) = p H ERR + (1-p) H 12 H ERR

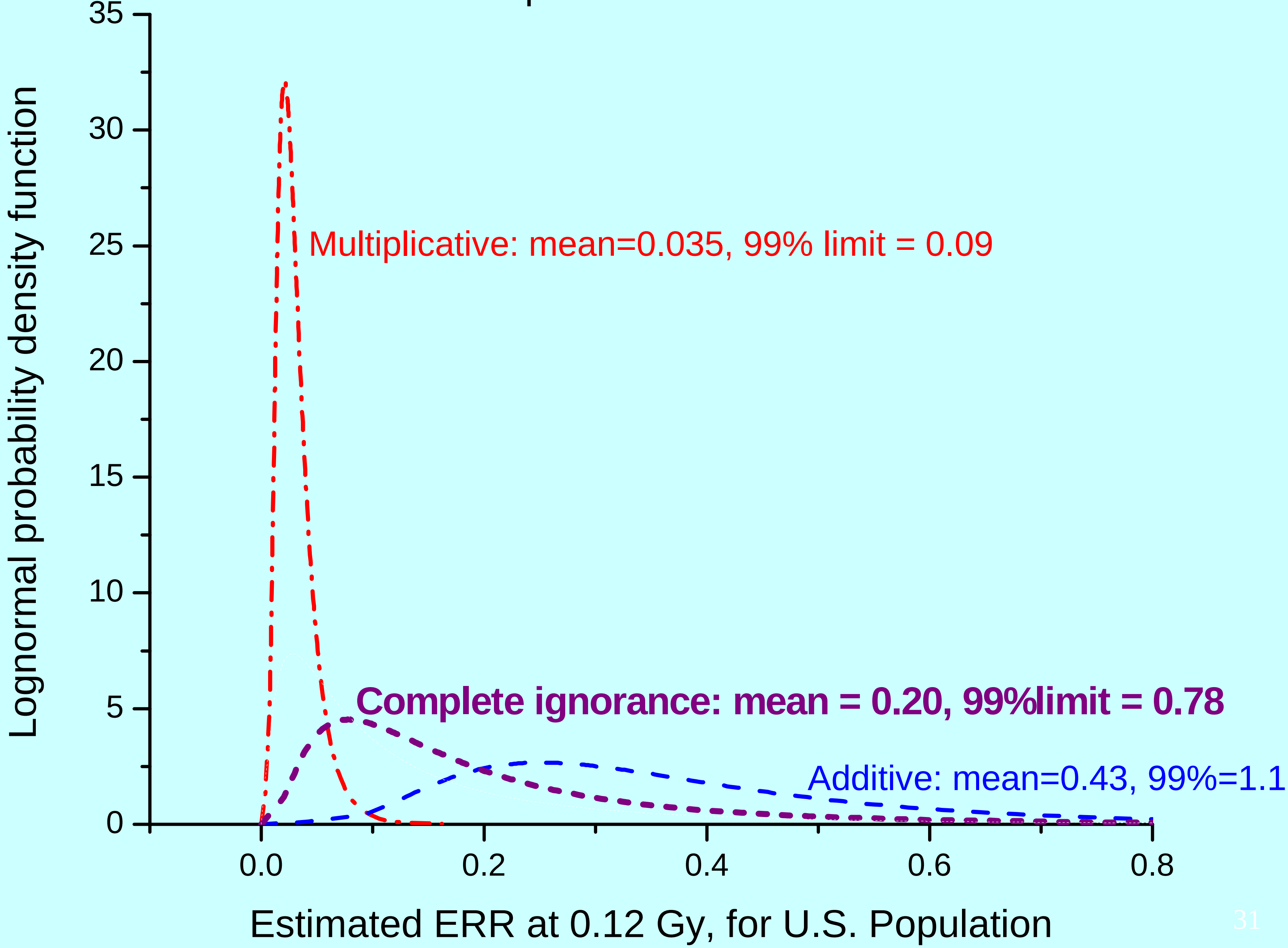
If we lack information, we might treat all such values of p as equally likely

- I.e., treat p as a (modified) uniform (0,1) random variable

"Ignorant" uncertainty distribution for linear mixture, pA+(1-p)M, of simple additive (p=1) and simple multiplicative (p=0) population transfer models.



Stomach Cancer Example: Comparison of ERR Uncertainty Distributions for Different Japan-to-US Transfer Models



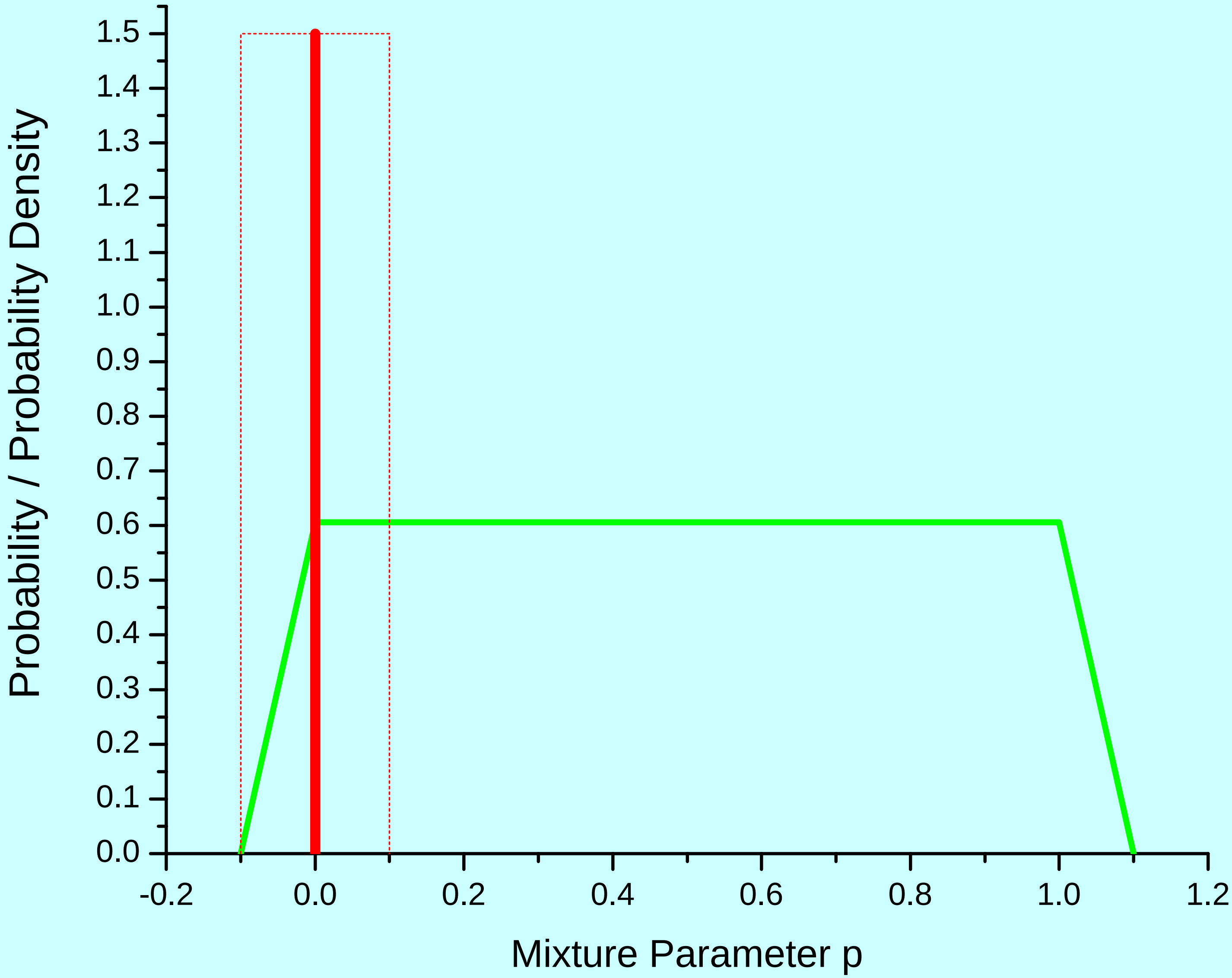
Gastric Cancer

We have **some** information indicating that ERR per Sv is similar in the US and Japan, despite the 12-fold greater baseline risk in Japan.

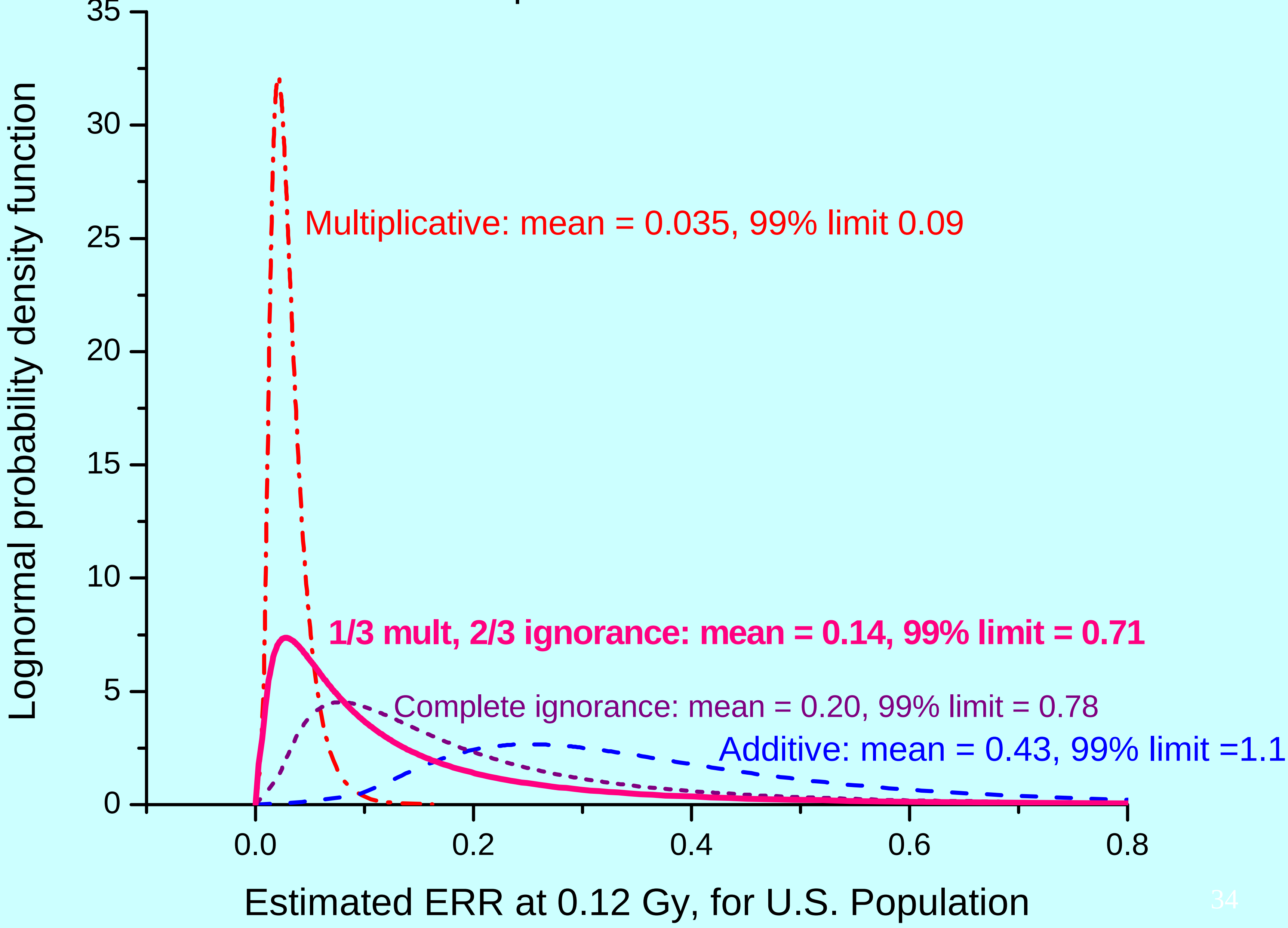
This information is not overwhelming,

Leading us to put 1/3 subjective weight on multiplicative transfer and 2/3 on ignorance.

Uncertainty Distribution of Stomach Cancer Mixture Parameter: 0.33 probability on p=0 (multiplicative transfer) and 0.67 on "ignorance"



Stomach Cancer Example: Comparison of ERR Uncertainty Distributions for Different Japan-to-US Transfer Models



In this example, the final ERR estimate has mean 0.14

And upper 99% probability limit 0.71

Because the upper limit for ERR is < 1, the upper limit for AS = ERR/(1+ERR) is < 0.5, and the claim would not be awarded

If the radiation had been diagnostic x ray, the claim would have been awarded.

- The uncertainties highlighted in the example are not academic
- In this example, the dominant uncertainty (78% of the total) concerns transfer between populations
- It is unfortunate that we know so little about this question
- In other examples, other factors (e.g., DDREF) may be more important

Extension to Lifetime Risk

A non-exposed US woman has, at age 30, a 0.7% expected lifetime risk of stomach cancer

In the example, the point (mean) estimate of excess lifetime risk is 0.14 H 0.7% = 0.1%

The 99% limit is 0.71 H 0.7% = 0.5%

- unlikely that total risk > 0.7% + 0.5% = 1.2%

95% limit is 0.44 H 0.7% = 0.3%

- 5% chance that exposure actually increases lifetime risk from 0.7% to $ 1.0%

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Main Accomplishments

Comprehensive uncertainty analysis

- Satisfies a societal requirement
- Clarifies risk estimation, highlights research needs

Interactive program (IREP)

- Makes things much easier
- Can be modified to incorporate new models, data, expert committee reports (e.g., BEIR VII)
- Is being adapted to estimate lifetime risk